REMARKS

Claims 35 and 37-39 are pending. Claims 1-34, 36, and 40-45 have been withdrawn.

Objections to the Specification

The specification has been objected to because:

1. "4H" was omitted from the series 4A through 4I at page 5, line 14;

2. Figure 8C is not described in the BRIEF DESCRIPTION OF THE DRAWINGS; and

3. The descriptions of the series of figures 4A-I and 5A-F refer to the spatial organization of the figures on the page and do not correspond to the organization of the figures on the page.

The specification has been amended in response to these objections and, therefore, the objections should be withdrawn.

Claim Rejections Under 35 U.S.C. § 103

Claims 35 and 37-39 have been rejected under 35 U.S.C. § 103(a) as obvious over Wong et al., J Immunother. 1998;21(1):32-40 ("Wong") in view of Khanna et al., Immuno Rev. 1999;170:49-64 ("Khanna 1999") and/or Khanna et al., Intern Immun. 1997;9(10):1537-1543 ("Khanna 1997").

The Examiner contends that Wong discloses a method in which a dendritic cell contacted with the EBV latent antigen LMP2a elicited a robust memory cytotoxic T-lymphocyte ("CTL") response. According to the Examiner, Khanna 1999; and Rickenson AB and Kieff E., "Epstein-Barr Virus," FIELDS VIROLOGY 3d Ed. 1996, page 2436 ("Rickenson") disclose that the potential EBV target antigens for CTL recognition are limited to the three predominate, latency-associated antigens EBNA1, LMP1 and LMP2. Further, the Examiner contends that Khanna 1997 discloses CTLs sensitized with EBNA-1 efficiently recognize EBV-transformed B cells.

The Examiner concludes that one of ordinary skill in the art would have been motivated to substitute EBNA-1 for LMP-2a because it was widely recognized that EBNA-1 is one of the primary latency-associated antigens. Further, according to the Examiner, priming CTLs with

EBNA-1 pulsed dendritic cells "would be an effective strategy to generate a CTL response to EBV-transformed B cells through their expression of EBNA-1 during latency." The Examiner concludes that one of ordinary skill in the art would have "expected to be able to make" an EBV-protective dendritic cell by substituting EBNA-1 for LMP2a because the technique for creating antigen-pulsed dendritic cells was well established and Wong discloses methods for making such cells using EBV latency-associated antigens.

None of the references cited with Wong would have provided one of ordinary skill in the art with a reasonable expectation that an EBNA-1 contacted human dendritic cell would be protective against EBV.

Khanna 1999 only discloses that EBNA1, LMP1 and LMP2 are "*potential* target antigens for CTL recognition" (Khanna 1999, page 60) (emphasis added). Khanna 1999 does not disclose or suggest a human dendritic cell pulsed with EBNA-1 that is protective against EBV. Khanna 1999 discloses that in an "[e]xtensive analysis of CTL responses in a large panel of healthy virus carriers....no reactivity towards EBNA1 was detected..." (Khanna 1999, page 51) (emphasis added). Khanna 1999 states that the glycine-alanine repeat sequences within EBNA1 have an inhibitory effect on endogenous processing of EBNA1 through the class I pathway, which "may on occasion be overridden *in vivo,* since...EBNA1-specific CTLs have been detected in healthy virus carriers. *Interestingly, these EBNA1-specific CTLs can only recognize LCLs to which recombinant EBNA1 protein has been supplied exogenously*" (Khanna 1999, page 51) (emphasis added). Thus, Khanna 1999 suggests that CTLs would (1) not react to an EBNA-1 contacted dendritic cell or, (2) if a CTL did react with such a dendritic cell, the resulting CTL would only recognize target cells to which *recombinant* EBNA-1 has been supplied. Neither of these scenarios provides any expectation that a dendritic cell pulsed with EBNA-1 would successfully protect against EBV infection. Furthermore, the absence of CTL responses to EBNA-1 in most healthy virus carriers suggests that immunity to EBNA-1 has no protective value.

Rickenson does not provide a reasonable expectation of success for an EBNA-1 contacted human dendritic cell protective against EBV. According to Rickenson, relative to other EBV-associated malignancies, the possibility of CTL-based therapy for nasopharyngeal cancer, Hodgkin's disease and T-cell lymphomas is "[e]ven more interesting, and more challenging"

because "the form of viral latency in these malignancies is such that many of the dominant antigens against which the virus-induced memory T-cell response is naturally directed....are not expressed in tumor cells. Therapeutic strategies must therefore seek to identify and exploit CTL responses which may be minor components of memory, but which are directed against epitopes in EBNA1 (if such exist), LMP1, or LMP2" (Rickenson, pages 2435-36). Thus, Rickenson discloses that it would be especially challenging to develop CTL-based therapy for EBV-associated malignancies that only express latent antigens, which *may* be *minor* components of memory. Further, Rickenson questions whether EBNA-1 epitopes *even exist*. Rickenson falls far short of providing a reasonable expectation of success for a human dendritic cell contacted with EBNA-1 that is protective against EBV infection. On the contrary, this reference creates a great deal of doubt as to whether the invention would work.

Khanna 1997 does not disclose or suggest a human dendritic cell contacted with EBNA-1 that is protective against EBV. According to Khanna 1997, "there is now convincing evidence to suggest that EBNA1 is *not* recognized by MHC class I-restricted cytotoxic T lymphocytes (CTL)" (Khanna 1997 abstract) (emphasis added). Khanna 1997 states that "we have recently shown that EBNA1 includes a sequence which can be presented by class II molecules and CTL specific for this epitope were isolated from a healthy seropositive donor. Interestingly, these CTL are unable to lyse EBV-infected B cells, suggesting that EBNA1 may not be endogenously processed and/or presented to the host CTL response" (Khanna 1997, page 1538, 1st column, 1st full paragraph). Khanna 1997 suggests only "a possibility" of immune targeting class I processing defective EBV-associated malignancies (Khanna 1997, page 1542, 2nd column), though it is hard to see even a possibility if CTLs could not recognize EBNA-1.

In sum, Khanna 1997 does not disclose or suggest a human dendritic cell contacted with EBNA-1 that is protective against EBV because, according to Khanna, (1) MHC class-I restricted T lymphocytes do not recognize EBNA-1 and (2) CTLs that do recognize an epitope of EBNA-1 are unable to lyse EBV-infected target cells. Thus, the reference provides no motivation to make the claimed EBNA-1 contacted dendritic cell because, according to the results it describes, such a dendritic cell would have no value since no protection is afforded against EBV infection by EBNA-1-specific CTLs that either do not "see" or see but cannot destroy EBV-infected cells.

Accordingly, the rejections under 35 U.S.C. § 103(a) should be withdrawn.

Conclusion

No new matter has been added. All of the pending claims in this application are believed to be in condition for allowance. Entry and consideration of these amendments and remarks are therefore respectfully requested.

Respectfully submitted,

Dated: October 12, 2004

By _____

Paul M. Zagar, M.D.
Registration No.: 52,392
DARBY & DARBY P.C.
P.O. Box 5257
New York, New York 10150-5257
(212) 527-7700
(212) 753-6237 (Fax)
Attorneys/Agents For Applicant